Close cooperation between infectious disease physicians and attending physicians can result in better management and outcome for patients with *Staphylococcus aureus* bacteraemia

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Abstract

Staphylococcus aureus bacteraemia (SAB) is a serious infection that demands prompt clinical attention for good outcome. To assess the impact of intervention by infectious diseases physicians (IDPs) in cases with SAB, a retrospective cohort study of patients with SAB was performed in a 1240-bed, university hospital in Japan, with the aim of comparing the management and outcome of patients during the initial and the latter half of the intervention period,. Three hundred and forty-six patients with SAB during the 7-year period, from 2002 to 2008, were included, and 194 patients in the initial half of the period (from 2002 to 2005) were compared with 152 patients in the later period (from 2006 to 2008). There was no significant difference between the two groups with respect to patient's clinical background, although more patients in the later period were receiving immunosuppressive treatment. The proportion of methicillin resistant *S. aureus* was lower during the later period (56.2% vs. 43.3%; p 0.02). Echocardiography was used more frequently (37.1% vs. 64.5%; p < 0.001). Infective endocarditis and metastatic infections were diagnosed more frequently (10.8% vs. 20.4%; p 0.01). Follow-up blood cultures were obtained more regularly (52.1% vs. 73.7%; p <0.001) and therapy was more frequently administered for at least 14 days (47.4% vs. 82.2%; p <0.001). The 30-day mortality improved during the intervention period (25.8% vs. 16.4%; p 0.04). The total number of blood cultures received by the laboratory increased annually and the total number of consultations increased by approximately 1.6-fold compared to 2002. Proactive intervention by IDPs raised awareness of optimal management of bacteraemia and improved the adherence to the standards of care, which subsequently resulted in an improvement in the outcome.

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Introduction

Infectious diseases are major causes of morbidity and mortality and contribute to increased healthcare costs. Clinical intervention by a multidisciplinary infection control team including infectious disease physicians (IDPs) reduces hospitalization duration and treatment costs for infected patients [1–3]. Although some studies suggest that intervention by IDPs can improve the quality of management of infectious disease [4–7], there is little evidence available to confirm that such intervention improves survival.

Antibiotics are prescribed by attending physicians (rather than by specialist IDPs) in Japan, as they are in most European countries. In addition, few hospitals have infectious diseases departments and IDPs are not routinely consulted about patients with bloodstream infection (BSI). In 2002, we started a hospital-wide, active clinical intervention by IDPs for the treatment of all bacteraemic patients at our hospital and found that mandatory intervention to treat candida BSI improves prognosis [8]. In addition to mandatory intervention for bacteraemia, IDP consultations are initiated by request from an attending physician or by an IDP when laboratory findings and the results of therapeutic drug monitor-

ing are significant, or when a specific antimicrobial agent is prescribed.

Staphylococcus aureus bacteraemia causes considerable morbidity and mortality in the hospital setting, and strategies to improve the management and outcome of this condition are needed [1,9,10]. Jenkins *et al.* [10,11] reported that mandatory intervention by IDPs improves adherence, although they did not demonstrate a statistically significant improvement in outcomes, possibly as a result of inadequate statistical power.

In the present study, we assessed the impact of 7 years of systematic intervention and report distinct improvements with respect to evaluation, treatment and outcome in patients with *S. aureus* bacteraemia.

Materials and methods

Study setting and population

The study took place at Kyoto University Hospital, which is a 1240-bed tertiary hospital that admits 340 000 patients/year. Approximately 400–600 nosocomial BSIs are treated at this hospital annually and *S. aureus* is the second most common cause (after coagulase-negative staphylococci) accounting for approximately 10% of BSI.

This retrospective cohort study compared the outcomes of all patients with *S. aureus* bacteraemia between the initial and the latter halves of an intervention period. Patients were included if they had proven *S. aureus* bacteraemia, which was defined as at least one *S. aureus*-positive blood culture plus a systemic inflammatory response. Patients with actual re-infection (rather than relapse) could be included several times. Data were excluded from analysis when patient survival or death could not be confirmed by medical records. The study periods comprised initial and later intervention periods from 2002–2005, and from 2006–2008, respectively. Data included age, sex, underlying conditions, location of acquisition, primary focus, timing of antibiotic initiation, complications and survival at 30 days after detection of *S. aureus* in blood cultures.

Intervention

Mandatory intervention began in 2002. Six IDPs from the Department of Infection Control and Prevention at Kyoto University Hospital were immediately informed of a positive blood culture. An IDP immediately assumed responsibility for a patient with clusters of Gram-positive cocci in blood cultures and provided recommendations directly to the attending physician regarding appropriate antibiotic therapy (i.e. choice of drug including glycopeptides, dose regimen and treatment period) and optimal management of the infection. The content and validity of all interventions were discussed at weekly meetings involving all IDPs with an independent assessor. Catheter-related infection was defined if the catheter tip grew $>1 \times 10^3$ colonies of *S. aureus* in the absence of an alternative source of infection. The modified Duke criteria were applied to all suspected cases of infective endocarditis [12,13].

Standards for the management of *S. aureus* bacteraemia

We developed key standards of care to evaluate and manage *S. aureus* bacteraemia, which comprised: obtaining blood for follow-up cultures within 5 days; administration of at least 14 days of antibiotic therapy for the bacteraemia; and investigation for infective endocarditis by echocardiography. Further evaluations, such as radiographic studies, were recommended to the attending physicians if clinical resolution was delayed regardless of appropriate antibiotic therapy. Practical 14- and 28-day regimens for uncomplicated and complicated patients, respectively, were determined on the basis of current guidelines and recent literature [14–16]. However, because the optimal treatment and appropriate classification of *S. aureus* bacteraemia remain undefined, we established 14 days as the minimal duration of therapy.

Assessment of general effects of the mandatory intervention in cases of bacteraemia

We reviewed the numbers of blood cultures received by the laboratory from any patients during the study period and the trends of all consultations recorded by the Department of Infection Control and Prevention in a database, as indicators of general effects on laboratory use and liaison with IDPs. Each consultation record was classified as 'consultation with attending physician', 'significant laboratory results', 'antibiotic prescription' and 'other' when the intervention started.

Statistical analysis

For bivariate analyses, categorical variables were compared by Fisher's exact test and an unpaired *t*-test where appropriate. The cumulative survival time between the day of the first blood culture results that were positive for *S. aureus* and death or the last outpatient clinic visit during the study period was calculated by the Kaplan–Meier method for all patients. The difference in 30-day cumulative survival of patients was tested by the Mantel–Cox test. The potential factors associated with 30-day mortality of patients were examined by the Cox proportional hazards regression analysis. All covariates that differed significantly between the initial intervention period and the later intervention period in the bivariate analysis were considered for model entry into the

above mentioned multivariate analyses. Data were analyzed with PASW for windows, version 18.0 (SPSS Inc., Chicago, IL, USA). All p values were two-tailed and p <0.05 was considered statistically significant.

Results

We reviewed the results from 346 patients with initially *S. aureus*-positive blood cultures. The initial and the latter intervention periods included 194 and 152 patients, respectively. Table 1 shows that the patients' demographic characteristics and comorbidities were generally similar between the two periods, although the proportion of methicillin-resistant *S. aureus* (MRSA) was lower during the later intervention period (56.2% vs. 43.3%; p 0.02), and the proportion of patients who received immunosuppressants was higher during the later period (19.6% vs. 28.9%; p 0.05).

Table 2 compares the two periods in terms of details of the infection process, the clinical management and the 30-day mortality. Echocardiography was applied more frequently (37.1% vs. 64.5%; p <0.001), which led to the discovery of more valvular vegetations (seven vs. ten patients) during the later period. Infective endocarditis or early metastatic infection was identified more frequently (10.8% vs. 20.4%; p 0.01). Follow-up blood samples for culture were obtained more regularly (52.1% vs. 73.7%; p <0.001), and therapy was more frequently administered for at least 14 days (47.4% vs. 82.2%; p <0.001). More patients with MRSA bacteraemia received anti-MRSA drugs (vancomycin, teicoplanin or arbekacin) within 2 days of blood cultures being obtained (64.2% vs. 89.4%; p <0.001).

The number of blood cultures increased annually to 1.7-fold more that that obtained at the beginning of the study period and the number of consultations also increased by approximately 1.6-fold compared to 2002. The growth rate in the number of consultations was higher for 'consultation with attending physicians' than for 'significant laboratory results' (Fig. 1).

The 30-day mortality decreased from 25.8% during the initial intervention period to 16.4% during the later intervention period (p 0.04 by the Mantel–Cox test) (Fig. 2). The results of Cox multivariate regression analysis suggested that appropriate timing of anti-MRSA drug, follow-up blood culture obtained, echocardiogram obtained and later intervention period remained as a predictor for 30-day mortality (Table 3).

Discussion

The present study has demonstrated that the setting up of a system with mandatory involvement of IDPs can improve the management and outcome in patients with *S. aureus* bacteraemia. Although, throughout the period of the investigation, IDPs were informed of cases by the laboratory and were therefore able to intervene with advice, including details of the approved regimen, they do not themselves order investigations or prescribe antibiotics. Therefore, the effectiveness of their mandatory involvement depends on building a relationship of confidence and trust. We consider that this contributed to the improved results obtained in the second period. The detailed evaluation of patients probably increased the recognition of infective endocarditis and metastatic infection [10]. This suggests that instances of endocarditis and metastatic infection remained undiagnosed and were treated as uncomplicated infections before consistent consultation was established. The rate of detected complica-

TABLE 1. Microbiological characteristics of causative isolates and clinical background of patients with *Staphylococcus aureus* bacteraemia according to intervention period

	2002–2005 (*n* = 194) Initial intervention period		2006–2008 (*n* = 152) Later intervention period		p
Age	62.1 ± 18.2		63.2 ± 16.8		0.78
Female sex	73	37.6%	63	41.4%	0.50
Risk factor					
Diabetes mellitus	42	21.6%	24	15.8%	0.21
Immunosuppressant	38	19.6%	44	28.9%	0.05
Haemodialysis	12	6.2%	9	5.9%	>0.99
Malignancy	35	18.0%	29	23.6%	0.88
Post transplantation	28	14.4%	13	8.6%	0.97
Hospitalized in intensive care unit	18	9.3%	19	12.5%	0.38
Management provider at time of bacteraemia					
Surgical	100	51.5%	72	47.4%	0.45
Medical	75	38.7%	62	40.8%	0.73
Paediatric	17	8.8%	24	15.8%	0.06
Obstetrics and gynaecology	2	1.0%	3	2.0%	0.65
Methicillin-resistant isolates	109	56.2%	66	43.4%	0.02

TABLE 2. Evaluation and classification of *Staphylococcus aureus* bacteraemia and complications according to intervention period

	2002–2005 (*n* = 194) Initial intervention period		2006–2008 (*n* = 152) Later intervention period		p
Primary source of infection					
Intravascular catheter	64	33.0%	60	39.5%	0.26
Skin and/or soft tissue	42	21.6%	33	21.7%	>0.99
Respiratory tract	9	4.6%	12	7.9%	0.26
Other	10	5.2%	6	3.9%	0.80
Unknown	69	35.6%	41	27.0%	0.10
Infective endocarditis	7	3.6%	10	6.6%	0.22
Metastatic infection	14	7.2%	21	13.8%	0.05
Endocarditis or metastatic infection	21	10.8%	31	20.4%	0.01
Vertebral osteomyelitis	7	3.6%	12	7.9%	0.09
Deep-tissue infection or abscess	2	1.0%	3	2.0%	0.66
Septic pulmonary emboli	3	1.5%	4	2.6%	0.70
Septic arthritis	2	1.0%	2	1.3%	>0.99
Appropriate timing of anti-MRSA drug within 2 days	70/109	64.2%	59/66	89.4%	<0.001
Follow-up blood culture obtained	101	52.1%	112	73.7%	<0.001
Days of therapy ≥ 14	92	47.4%	125	82.2%	<0.001
Echocardiogram obtained	72	37.1%	98	64.5%	<0.001
30-Day mortality	50	25.8%	25	16.4%	0.04
MSSA	14/85	16.5%	11/86	12.8%	0.52
MRSA	36/109	33.0%	14/66	21.2%	0.12

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

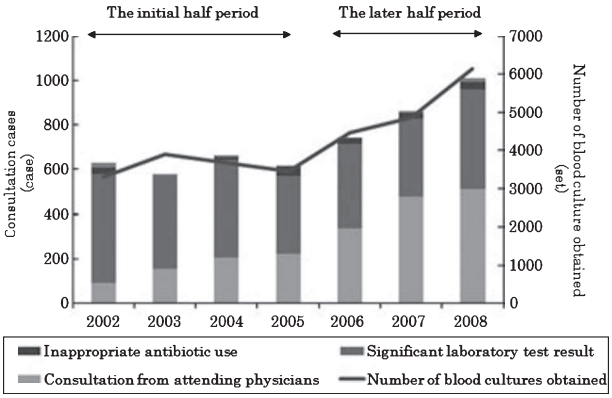

FIG. 1. Trends of characteristics of consultations (bars) and number of blood cultures obtained (solid line). The number of blood cultures increased annually to 1.7-fold more than that obtained at the beginning of the study period, and the number of consultations also increased by approximately 1.6-fold compared to 2002. Growth rate in number of consultations was higher for 'consultation with attending physicians' than for 'significant laboratory results'.

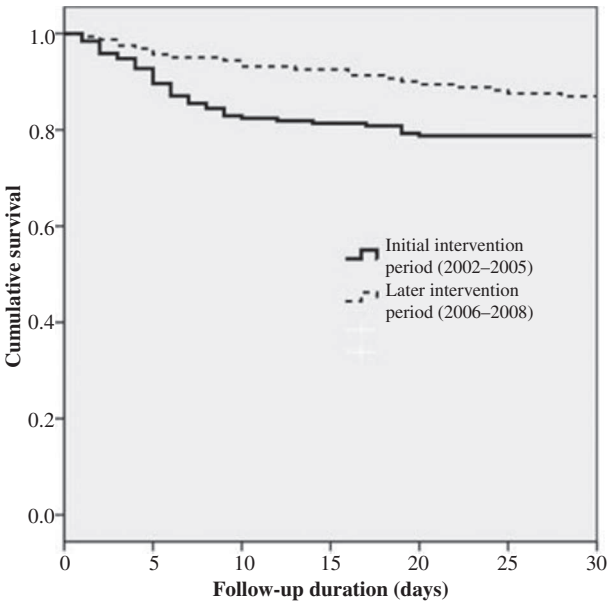

FIG. 2. Kaplain–Meier survival curves (at 30 days) for patients in the first period and the second period (Mantel–Cox test: p 0.04).

tions during the initial intervention period was low. If the actual incidence of complications did not differ during the whole study period, it is likely that one reason for the improved prognosis during the second phase is that more complications were recognized, and thus more patients were appropriately treated during this latter intervention period.

Another reason for the improved prognosis could be the lower proportion of methicillin-resistant isolates. One study has suggested that the mortality of MRSA bacteraemia is higher than that of methicillin-susceptible *S. aureus* (MSSA) bacteraemia [17]. However, the better overall prognosis cannot be fully explained only by a reduction in the numbers of resistant pathogens. In addition, 30-day mortality improved, despite the higher proportion of patients receiving immunosuppressants during the latter period.

The improved outcome in patients with MRSA bacteraemia might be derived from the earlier administration of optimal antibiotics during the second period. Several prospective studies have shown that inadequate antibiotic

TABLE 3. Predictors of 30-day mortality (Cox multivariate analysis)

Predictor	Adjusted hazards ratio (95% CI)	p
Pediatrics	0.69 (0.27–1.74)	0.43
Immunosuppressant	1.37 (0.75–2.49)	0.31
Methicillin resistant	1.27 (0.79–2.07)	0.33
Appropriate timing of anti-MRSA drug within 2 days	0.79 (0.31–1.36)	0.08
Follow-up blood culture obtained	1.12 (0.35–1.93)	0.09
Days of therapy ≥ 14	0.57 (0.30–0.98)	0.08
Echocardiogram obtained	0.65 (0.33–1.26)	0.33
Calendar year	0.99 (0.78–1.12)	0.85
Later period (2006–2008)	0.60 (0.30–0.89)	0.02

MRSA, methicillin-resistant *Staphylococcus aureus*.

therapy is a significant risk factor for mortality resulting from *S. aureus* bacteraemia, with inadequate therapy being more frequent in MRSA than in MSSA bacteraemia [18,19]. Lodise *et al.* [20] reported that a delay in administering correct therapy beyond a breakpoint as late as 45 h after obtaining blood cultures is an independent predictor of infection-related mortality. We essentially recommend the use of glycopeptides when Gram stains of positive blood cultures reveal Gram-positive clusters of cocci because over 60% of clinical staphylococcal isolates are methicillin-resistant at our hospital. Aggressive treatment and optimal management strategies are central to the management of *S. aureus* bacteraemia [21,22] and the earlier initiation of anti-MRSA drugs may have substantially contributed to the improved prognosis in the present study. The value of intervention by IDPs can be more readily assessed in patients with staphylococcal bacteraemia as a result of the crtical therapeutic decision to administer glycopeptides in this situation, whereas the impact of IDP intervention on antibiotic use against Gram-negative bacteraemia may be difficult to demonstrate because broad-range antibiotics are empirically administered to many septic patients.

Our policy of active intervention resulted in a general increase in the number of consultations with attending physicians. The significant increase in the number of blood cultures and changes in consultation trends suggest that attending physicians have become more cognisant of the concept of optimal therapies for infectious diseases and the usefulness of IDP advice. The present study demonstrates that the increased acceptance of such an intervention by attending physicians can improve subsequent outcomes of patients with *S. aureus* bacteraemia.

Limitations that are generally inherent in historical cohort studies apply to the present study. A potential confounding effect exists because we compared findings from two consecutive periods, and there may have been other factors influencing the differences observed. However, no major changes such as the introduction of a new anti-MRSA drug for treating *S. aureus* bacteraemia occurred during the study period. We eliminated selection bias by including all patients with *S. aureus* bacteraemia who presented at our hospital during the study. Possible changes in practice that were not evaluated in the present study, such as the management of therapeutic drug monitoring for anti-MRSA drugs or the administration of optimal antimicrobial therapy against concomitant infection as a result of our intervention, might have affected patient prognosis in some way. The effects of such changes, however, could be considered part of the benefit derived from active IDP involvement.

Proactive intervention by IDPs raised awareness of the optimal management of bacteraemia and improved adherence to the standard of care for patients with *S. aureus* bacteraemia, which subsequently resulted in an improved outcome.

Transparency Declaration

All authors report no conflicts of interest relevant to this article.

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